Effect of Neoadjuvant Iodine-125 Brachytherapy Upon Resection of Glioma

Congxiao Wang

the Affiliated Hospital of Qingdao University

Chao Liu

Pingyi People's Hospital

Han Jiang

Qingdao Medical College of Qingdao University

Wei Zhang

the Affiliated Hospital of Qingdao University

Lili Yang

the Affiliated Hospital of Qingdao University

Xueda Li

the Affiliated Hospital of Qingdao University

Zixiang Li

the Affiliated Hospital of Qingdao University

Lijing Peng

the Affiliated Hospital of Qingdao University

Xiaokun Hu

the Affiliated Hospital of Qingdao University

Peng Sun (✉ sunpeng@qdu.edu.cn)

the Affiliated Hospital of Qingdao University

Research Article

Keywords: Neoadjuvant 125I brachytherapy, Glioma, Surgical resection, Combination therapy, Tumor Shrinkage

Posted Date: January 11th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1155190/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Cancer on April 12th, 2022. See the published version at <https://doi.org/10.1186/s12885-022-09504-5>.

Abstract

Background: A more extensive surgical resection of glioma contributes to improved overall survival (OS) and progression-free survival (PFS). However, some of the patients lost the chance of surgical resection when the tumor involves critical structures.

Purpose: The present study aimed to assess the feasibility of neoadjuvant ^{125}I brachytherapy followed by total gross resection for initially inoperable glioma.

Methods: Six patients diagnosed with inoperable glioma due to invasion of eloquent areas, bi-hemispheric diffusion, or large tumor volume received ^{125}I brachytherapy. Surgical resection was performed when the tumor shrank, allowing a safe resection, assessed by the neurosurgeons. Patients were followed up after surgery.

Results: Tumor shrinkage after adjuvant ^{125}I brachytherapy enabled a total gross resection of all six patients. Four patients were still alive at the last follow-up, with the longest survival time of more than 50 months, two of which returned to a normal life with the KPS of 100. Another two patients got a neurological injury with the KPS of 80 and 50, respectively. One patient with grade IV glioma died 34 months, and another patient with grade IV glioma died 40 months later after the combined therapy.

Conclusions: In the present study, the results demonstrated that ^{125}I brachytherapy enabled a complete resection of patients with initially unresectable gliomas. ^{125}I brachytherapy may offer a proper neoadjuvant therapy method for glioma.

Background

Gliomas are thought to originate from glial, stem, or neuronal precursor cells. According to histology, World Health Organization (WHO) classified glioma into four different grades (grade I-IV). Usually, grade I to III gliomas are called low-grade gliomas, and grade IV and III gliomas are called high-grade or malignant gliomas[1]. For glioma, surgical resection was the first option.[1, 2] Numerous data confirmed the therapeutic efficacy of maximal possible surgical resection avoiding neurological damages in improving progression-free survival (PFS) and overall survival (OS). However, due to the situation of eloquent areas, bi-hemispheric diffusion, or large volume limitation, the extent of resection (EOR) is limited[1, 3]. Recent studies suggested that preoperative chemotherapy could decrease the tumor volume, thereby facilitating a safe and extensive resection[4, 5], which could prolong the PFS and OS of patients with gliomas.

Gliomas easily recur due to the characteristic of diffusely infiltrating spread from the origin site [6, 7]. Based on the characteristics, the local treatment with ^{125}I is possible. Brachytherapy with iodine-125 seeds offered a safe and effective local treatment option for patients, including glioma located in the eloquent brain[8–11]. Furthermore, ^{125}I brachytherapy showed advantages on the tumor shrinkage as the

^{125}I seeds were inserted within the tumors, continuously releasing γ rays. However, the feasibility of the therapy strategy, combining neoadjuvant ^{125}I brachytherapy with followed surgical resection, has never been thoroughly evaluated to our best knowledge. Thus, we undertook the present study to assess whether neoadjuvant ^{125}I brachytherapy could facilitate a safe total gross resection for patients with initially unresectable gliomas and whether the combination therapy is effective.

Methods

All methods were performed in accordance with the relevant guidelines and regulations.

Patient Criteria

Patients' data were obtained from the database of hospital, spanned from January 1, 2016, to December 31, 2017. The retrospective study was approved by the Institutional Review Board of the local hospital (Reference number: QYFY WZ LL 26579) with the informed consent waived. The inclusion criteria were as follows: (1) Age ≥ 18 years old; (2) Enhanced MRI or CT deemed unresectable gliomas upon neurosurgical evaluation; (3) Combined therapeutic approach, consisting of neoadjuvant ^{125}I brachytherapy and subsequent surgical resection; (4) Availability of adequate laboratory examination information, including hematologic parameters, clotting, hepatic and renal function, etc. Patients with glioma involved in the brain stem or ependymal surface were excluded.

Iodine-125 Implantation

Iodine-125 seeds were implanted as we previously reported[11]. Briefly, patients were fixed on the CT bed safely with a negative pressure vacuum pad. Then, ^{125}I seeds were implanted according to the pre-implantation plan made with the computerized treatment planning system (TPS; Beijing Astro Technology Ltd. Co., Beijing, China). Patients were required to stay in bed for 24 hours, and dehydration medications were given for 7-14 days. After the implantation of the ^{125}I seeds, patients received outpatient examinations every two months. Examinations were evaluated by the neurosurgeons. Surgical resection was carried out when the glioma shrank to a suitable size.

Results

A total of two males and four females were included in this study. The median age was 46 years old (range 20-73). The median follow-up time from diagnosis was 32.5 months (range 21-47). The presenting symptoms were headache in three patients, nausea in one patient, vomit in one patient, dizziness in one patient, myodynamia decline in one patient, vision decline in one patient, language disorders in two patients, and seizures in five patients. The median KPS was 85 (range 70-90). The anatomical location of the tumor was frontal in four patients, parietal in one patient, and left hippocampus in one patient. Three

patients had low-grade gliomas, and the other three patients had high-grade gliomas. One patient had her first neuropathological diagnosis by biopsy; the other five patients were diagnosed with craniotomy. One patient with recurrent glioma received surgical resection accompanied by external beam radiotherapy (total dose 50Gy, 2Gy/time) and chemotherapy with Temozolomide (TMZ, 75mg/m²) before. One patient received Bevacizumab treatment (400mg/time, 4 times total) before. The other four patients received ¹²⁵I brachytherapy as initial therapy. ¹²⁵I seeds were implanted with TPS guidance, and verification of the dosage distribution was carried out immediately after the implantation (Fig. 1 and Fig. 2). All the patients received the total surgical resection after the ¹²⁵I brachytherapy with a median therapy interval of 6 months (range 2-23 months).

One patient with glioblastoma return to a normal life with a KPS of 100, who was still alive at the time of the last follow-up (Survival time=50 months) (Fig. 3 and Fig. 4). Another patient with grade II oligodendroglioma survived more than 51 months, with a KPS of 100, and was still alive at the time we followed up. No Neurological symptoms were found in these two patients after the combination of therapy. They were free from seizures after the combined therapy. Another two patients with grade III and II gliomas were alive at the time we followed up (survival time: 33months and 31 months respectively), with the KPS of 50 and 80, respectively. One patient (grade II gliomas) died with a survival time of 34 months. And, another patient with glioblastoma died with a survival time of 40 months.

Discussion

In the present study, we retrospectively analyzed patients with gliomas who were not suitable for surgical resection of the tumors. A gross total resection after a significant shrinkage of the tumor due to ¹²⁵I implantation was achieved in six cases, and the patients got a long survival time.

According to the European guidelines[2], surgery resection represents the first treatment option for gliomas, aiming to perform a maximal tumor mass resection and avoid long-term neurological deficits. However, gliomas located in the eloquent cortex, deep structure, and corpus callosum or with a large volume limited the extent of surgical resection, sometimes causing severe neurological deficits. Neoadjuvant therapy had been widely used in tumors downstage, which enabled a secondary resectability[12]. Neoadjuvant therapy had been successfully used in biliary tract cancer, intrahepatic cholangiocarcinoma, and hepatocellular carcinoma (HCC) [13–15]. Moreover, Marie Blonski and Jasmin Jo's studies confirmed that neoadjuvant Temozolomide therapy could shrink the tumor, which enables a surgical resection of gliomas [4, 5, 16]. ¹²⁵I brachytherapy was emerging as a new therapy approach for tumors[17–21] and also had been used in gliomas therapy, primarily as salvage therapy. ¹²⁵I brachytherapy showed effective local control of the gliomas. However, whether ¹²⁵I brachytherapy could be used as a neoadjuvant therapy approach for patients with unresectable gliomas was not explored.

In the present study, six patients received ¹²⁵I brachytherapy. Surgical resection was not suitable for these patients due to the location and volume of the tumors. Two patients received other therapies before, and

four patients received ^{125}I brachytherapy as initial therapy. Most patients showed noticeable tumor shrinkage 2-8 months after the ^{125}I brachytherapy regardless of the tumor type. After a complete evaluation by the neurosurgeon, the six patients received total surgical resection of tumors at different time points after ^{125}I brachytherapy. One patient with glioblastoma returned to a normal life after the combination of the therapy with a KPS of 100. No neurological system disorders were found after the therapy. Now the patient got married and had a baby. Another patient with grade III oligodendroglioma also got a KPS of 100 after therapy, and were free from seizure. Furthermore, at the time of the last follow-up, the patient was ready for marriage. The two patients discussed above all faced a large tumor volume before the surgery. After the therapy with ^{125}I , the tumor volume decreased, which enabled a total surgical resection. Among all the six patients received the combination therapy of ^{125}I brachytherapy followed by total surgical resection. Four of them were still alive at the time we last followed up, with a survival time of more than 31 months. Only one patient had language disorders after the therapy. Moreover, all the patients who survived were free from seizures. Two patients died with a survival time of more than 34 months.

The results showed that ^{125}I brachytherapy showed practical efficacy in tumor shrinkage, enabling a followed total surgical resection. No severe neurological damages were found after the combined therapy. Furthermore, patients were free from seizures after the therapy. All the patients survived a long time after the therapy. No matter for the recurrent or primary gliomas, the combination therapy showed obvious efficacy. However, only six patients were included in this study, among which included the low and high-grade gliomas. A large amount of cases should be included in further studies.

Conclusions

The results were not able to offer statistically significant. However, the results were positive and indicated a promising therapeutic approach for gliomas. Thus, we believed that neoadjuvant ^{125}I brachytherapy followed by surgical resection might give opportunities to patients with gliomas.

Abbreviations

CT: Computed Tomography

EOR: Extent of Resection

HCC: hepatocellular carcinoma

KPS: Karnofsky Performance Status

MRI: Magnetic Resonance Imaging

OS: Overall Survival

PFS: Progression-free survival

TMZ: Temozolomide

TPS: Treatment Planning System

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

This study has obtained IRB approval from the institutional review board of the Affiliated Hospital of Qingdao University, and the need for informed consent was waived

(Reference number: QYFY WZ LL 26579). The study was performed in accordance with the

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The data of the patients are available from the electronic medical record of the Affiliated Hospital of Qingdao University.

Competing interests

None

Funding

This work was supported by the the National Science Foundation for Youths of China (No. 81901800). China Postdoctoral Science Foundation (No. 2021M701812). Ministry of Science and Technology of the People's Republic of China (No. 2019YFE0120100) 中国医学教育协会 (No. 2020KTZ003).

Author's contributions

Congxiao Wang conducted all experiments, integrated data, edited figures, and wrote the manuscript; Chao Liu collected and arranged the data. Han Jiang, Wei Zhang, Lili Yang, Xueda Li, Zixiang Li, and Lijing Peng provided essential assistance; Peng Sun and Xiaokun Hu directed this study, designed the research, and gave key advice.

Acknowledgements:

None

References

1. Eyüpoglu IY, Buchfelder M, Savaskan NE: **Surgical resection of malignant gliomas—role in optimizing patient outcome.** *Nature Reviews Neurology* 2013, **9**(3):141–151.
2. Soffietti R, Baumert B, Bello L, Von Deimling A, Duffau H, Frénay M, Grisold W, Grant R, Graus F, Hoang-Xuan K: **Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force.** *European Journal of Neurology* 2010, **17**(9):1124–1133.
3. Duffau H, Capelle L: **Preferential brain locations of low-grade gliomas: Comparison with glioblastomas and review of hypothesis.** *Cancer* 2004, **100**(12):2622–2626.
4. Jo J, Williams B, Smolkin M, Wintermark M, Shaffrey ME, Lopes MB, Schiff D: **Effect of neoadjuvant temozolomide upon volume reduction and resection of diffuse low-grade glioma.** *Journal of neuro-oncology* 2014, **120**(1):155–161.
5. Blonski M, Taillandier L, Herbet G, Maldonado IL, Beauchesne P, Fabbro M, Campello C, Gozé C, Rigau V, Moritz-Gasser S: **Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life.** *Journal of neuro-oncology* 2012, **106**(2):353–366.
6. Hu X, Qiu H, Zhang L, Zhang W, Ma Y, Qiao Z, Chen D, Han J, Duan G, Zhang F: **Recurrent gliomas.** *Cancer Biology & Therapy* 2014, **13**(10):840–847.
7. Diamandis P, Aldape K: **World Health Organization 2016 Classification of Central Nervous System Tumors.** *Neurol Clin* 2018, **36**(3):439–447.
8. Schwarz SB, Thon N, Nikolajek K, Niyazi M, Tonn J-C, Belka C, Kreth F-W: **Iodine-125 brachytherapy for brain tumours—a review.** *Radiation Oncology* 2012, **7**(1):30.
9. Ruge MI, Kickingereider P, Simon T, Treuer H, Sturm V: **Stereotactic iodine-125 brachytherapy for treatment of inoperable focal brainstem gliomas of WHO grades I and II: feasibility and long-term outcome.** *Journal of Neuro-Oncology* 2012, **109**(2):273–283.
10. Ruge MI, Kickingereider P, Grau S, Dorn F, Galldiks N, Treuer H, Sturm V: **Stereotactic iodine-125 brachytherapy for the treatment of WHO grades II and III gliomas located in the central sulcus region.** *Neuro Oncol* 2013, **15**(12):1721–1731.

11. Wang C, Liu S, Peng L, Zhang K, Li W, Zhang H, Luan Y, Li P, Hu X: **Permanent iodine-125 brachytherapy for patients with progressive or recurrent high-grade gliomas.** *BMC Cancer* 2020, **20**(1):591.
12. Burotto M, Wilkerson J, Stein WD, Bates SE, Fojo T: **Adjuvant and neoadjuvant cancer therapies: a historical review and a rational approach to understand outcomes.** In: *Seminars in oncology: 2019.* Elsevier; 2019: 83–99.
13. Kato A, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Takeuchi D, Takayashiki T, Kimura F, Miyazaki M: **Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study.** *Annals of surgical oncology* 2013, **20**(1):318–324.
14. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, Vibert E, Castaing D, Adam R, Cherqui D: **Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma.** *British Journal of Surgery* 2018, **105**(7):839–847.
15. Shi F, Wu M, Lian S-S, Mo Z-Q, Gou Q, Xu R-D, Li H-L, Huang Z-M, Wu P-H, Chen X-M: **Radiofrequency ablation following downstaging of hepatocellular carcinoma by using transarterial chemoembolization: long-term outcomes.** *Radiology* 2019, **293**(3):707–715.
16. Blonski M, Pallud J, Gozé C, Mandonnet E, Rigau V, Bauchet L, Fabbro M, Beauchesne P, Baron M-H, Fontaine D: **Neoadjuvant chemotherapy may optimize the extent of resection of World Health Organization grade II gliomas: a case series of 17 patients.** *Journal of Neuro-oncology* 2013, **113**(2):267–275.
17. Kickingereder P, Hamisch C, Suchorska B, Galldiks N, Visser-Vandewalle V, Goldbrunner R, Kocher M, Treuer H, Voges J, Ruge MI: **Low-dose rate stereotactic iodine-125 brachytherapy for the treatment of inoperable primary and recurrent glioblastoma: single-center experience with 201 cases.** *Journal of Neuro-Oncology* 2014, **120**(3):615–623.
18. Yu Y-h, Wei C-y, Qin Q-h, Mo Q-g, Huang Z, Lian B: **Efficacy of Iodine-125 Seed Implantation in Locoregionally Recurrent and Unresectable Breast Cancer: a Retrospective Study.** *Pathology & Oncology Research* 2017, **25**(1):327–332.
19. He Y, Li L, Liu J, Zhang X: **Iodine-125 seed brachytherapy inhibits non-small cell lung cancer by suppressing epithelial-mesenchymal transition.** *Brachytherapy* 2018, **17**(4):696–701.
20. Chen K, Chen G, Wang H, Li H, Xiao J, Duan X, He J, He K, Xiang G: **Increased survival in hepatocellular carcinoma with iodine-125 implantation plus radiofrequency ablation: A prospective randomized controlled trial.** *Journal of Hepatology* 2014, **61**(6):1304–1311.
21. Zhang W, Li J, Li R, Zhang Y, Han M, Ma W: **Efficacy and safety of iodine-125 radioactive seeds brachytherapy for advanced non-small cell lung cancer—A meta-analysis.** *Brachytherapy* 2018, **17**(2):439–448.

Figures

Figure 1

Pre-implantation plan of ^{125}I brachytherapy for a patient with grade IV glioma (a) The gross target volume (GTV) was outlined with a red line, the clinical target volume (CTV) was outlined with a blue line. Different colored lines showed the dose distribution. Additionally, the needle paths were designed with TPS. (b) Pre-implantation dose volume histogram (DVH) of GTV and CTV. (c) Pre-implantation D100, D90, D80, V150, V100, V90 of the GTV and CTV.

Figure 2

Post-implantation verification of ^{125}I brachytherapy for a patient with grade IV glioma. (a-d) The gross target volume (GTV) was outlined with a red line, the clinical target volume (CTV) was outlined with a blue line. Different colored lines showed the dose distribution after ^{125}I implantation. (e-f) 3D-reconstruction of the CT-MRI infusion images after ^{125}I implantation. (g) Post-implantation DVH of GTV and CTV. (h) Post-implantation D100, D90, D80, V150, V100, V90 of the GTV and CTV.

Figure 3

Brain MR images of the patients with grade IV glioma. Apparent diffusion coefficient (ADC), diffusion weighted image (DWI), T1WI-contrast, and T2WI-flair images of the brain showed the occupation of the tumor, and severe brain edema around the glioma was showed on the images.

Figure 4

Brain MR images of the patients with grade IV glioma, 8 months after the ^{125}I implantation. ADC, DWI, T1WI-contrast, and T2WI-flair images showed the glioma shrink obviously after the ^{125}I implantation. The brain edema also improved compared with the brain images 8 months ago.